

MOHAMED 09/997,936

=> d his

(FILE 'HOME' ENTERED AT 09:49:49 ON 23 OCT 2003)

FILE 'HCAPLUS' ENTERED AT 09:49:58 ON 23 OCT 2003

L1 467 S BALASUBRAMANIAN S?/AU
L2 19 S BESMAN M?/AU
L3 17 S KASHI R?/AU
L4 126 S RAMANI K?/AU
L5 622 S L1-4
L6 1 S L5 AND AHF
SELECT RN L6 1

FILE 'REGISTRY' ENTERED AT 09:50:56 ON 23 OCT 2003

L7 10 S E1-10

FILE 'HCAPLUS' ENTERED AT 09:51:12 ON 23 OCT 2003

L8 1 S L6 AND L7

=> d ibib abs hitstr ind

L8 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2002:428652 HCAPLUS

DOCUMENT NUMBER: 137:10979

TITLE: Preparation of antihemophilic factor A-associated dispersion system

INVENTOR(S): Balasubramanian, Sathyamangalam V.;
Besman, Marc; Kashi, Ramesh;
Ramani, Karthik

PATENT ASSIGNEE(S): The Research Foundation of State University of New York, USA; Baxter Healthcare Corporation

SOURCE: PCT Int. Appl., 40 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|------|----------|-----------------|----------|
| WO 2002043665 | A2 | 20020606 | WO 2001-US48201 | 20011130 |
| WO 2002043665 | A3 | 20020711 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BC, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

| | | | | |
|---------------|----|----------|---------------|----------|
| AU 2002030607 | A5 | 20020611 | AU 2002-39607 | 20011130 |
|---------------|----|----------|---------------|----------|

| | | | | |
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| US 2002132982 | A1 | 20020919 | US 2001-997936 | 20011130 |
|---------------|----|----------|----------------|----------|

PRIORITY APPLN. INFO.: US 2000-250137P P 20001130

WO 2001-US48201 W 20011130

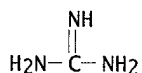
AB A method for complexing AHF (antihemophilic factor A) in a dispersed medium, includes: providing an AHF protein, altering the conformational state of the AHF protein to expose hydrophobic domains therein, binding a stabilizer to the exposed hydrophobic domains, and at least partially reversing the alteration to assoc. at least a portion of the protein with the stabilizer. A stabilized AHF dosage form, wherein >25% of the AHF mol., is assoc. with a stabilizer is also disclosed. DMPC, brain phosphatidylserines, and cholesterol were dissolved in chloroform and the solvent was removed. The multilamellar vesicles thus formed were filtered through a polycarbonate filter to form small unilamellar (SUVs) below 200 nm. The liposomes encapsulating the protein were formed by mixing the

liposomes in protein (AHF) contg. buffer and ethanol followed by gentle swirling .gtoreq.37.degree. to generate intermediate structures. The PEGylation of these particles were performed by adding DSPE-PEG.

IT 113189-02-9, Blood coagulation factor VIII
 RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (prepn. of antihemophilic factor A-assocd. dispersion system)
 RN 113189-02-9 HCAPLUS
 CN Blood-coagulation factor VIII, procoagulant (9CI) (CA INDEX NAME)

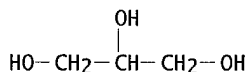
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 50-01-1, Guanidinium hydrochloride 56-81-5, Glycerol, processes 57-13-6, Urea, processes 64-17-5, Ethanol, processes 67-56-1, Methanol, processes 107-21-1, Ethylene glycol, processes
 RL: PEP (Physical, engineering or chemical process); PYP (Physical process); PROC (Process)
 (prepn. of antihemophilic factor A-assocd. dispersion system)
 RN 50-01-1 HCAPLUS
 CN Guanidine, monohydrochloride (8CI, 9CI) (CA INDEX NAME)

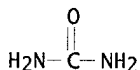


● HCl

RN 56-81-5 HCAPLUS
 CN 1,2,3-Propanetriol (9CI) (CA INDEX NAME)



RN 57-13-6 HCAPLUS
 CN Urea (8CI, 9CI) (CA INDEX NAME)



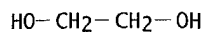
RN 64-17-5 HCAPLUS
 CN Ethanol (9CI) (CA INDEX NAME)



RN 67-56-1 HCAPLUS
 CN Methanol (8CI, 9CI) (CA INDEX NAME)

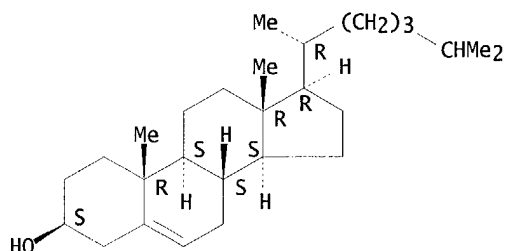


RN 107-21-1 HCAPLUS
 CN 1,2-Ethanediol (9CI) (CA INDEX NAME)

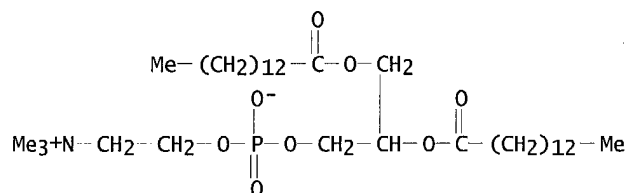


IT 57-88-5, Cholesterol, biological studies 18656-38-7,
 DMPC 145035-96-7, DSPE-PEG
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (prepn. of antihemophilic factor A-assocd. dispersion system)
 RN 57-88-5 HCAPLUS
 CN Cholest-5-en-3-ol (3.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

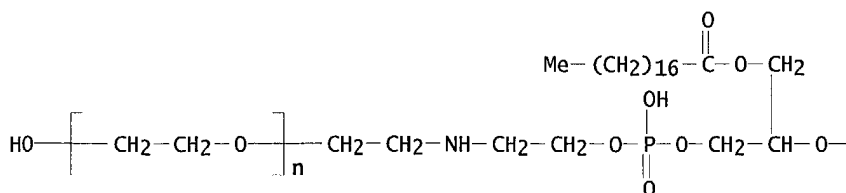


RN 18656-38-7 HCAPLUS
 CN 3,5,9-Trioxa-4-phosphatricosan-1-aminium, 4-hydroxy-N,N,N-trimethyl-10-oxo-7-[(1-oxotetradecyl)oxy]-, inner salt, 4-oxide (9CI) (CA INDEX NAME)

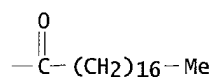


RN 145035-96-7 HCAPLUS
 CN Poly(oxy-1,2-ethanediyl), .alpha.-[7-hydroxy-7-oxido-13-oxo-10-[(1-oxooctadecyl)oxy]-6,8,12-trioxa-3-aza-7-phosphatriacont-1-yl]-.omega.-hydroxy- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B



IC ICM A61K

CC 63-6 (Pharmaceuticals)
 ST antihemophilic factor A dispersion liposome
 IT Polymers, biological studies
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (hydrophilic; prepn. of antihemophilic factor A-assocd. dispersion system)
 IT Drug delivery systems
 (liposomes; prepn. of antihemophilic factor A-assocd. dispersion system)
 IT Conformation
 Solvents
 Stabilizing agents
 (prepn. of antihemophilic factor A-assocd. dispersion system)
 IT Phosphatidylserines
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (prepn. of antihemophilic factor A-assocd. dispersion system)
 IT Denaturation
 Secondary structure
 (protein; prepn. of antihemophilic factor A-assocd. dispersion system)
 IT 113189-02-9, Blood coagulation factor VIII
 RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (prepn. of antihemophilic factor A-assocd. dispersion system)
 IT 50-01-1, Guanidinium hydrochloride 56-81-5, Glycerol, processes 57-13-6, Urea, processes 64-17-5, Ethanol, processes 67-56-1, Methanol, processes 107-21-1, Ethylene glycol, processes
 RL: PEP (Physical, engineering or chemical process); PYP (Physical process); PROC (Process)
 (prepn. of antihemophilic factor A-assocd. dispersion system)
 IT 57-88-5, Cholesterol, biological studies 18656-38-7, DMPC 145035-96-7, DSPE-PEG
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (prepn. of antihemophilic factor A-assocd. dispersion system)

=> file hcaplus
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FILE COVERS 1907 - 23 Oct 2003 VOL 139 ISS 17
 FILE LAST UPDATED: 22 Oct 2003 (20031022/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CT = controlled terms

PFT = old, new §,
 "used for" terms

NT = narrower term

OBI = all search fields
 except the abstract

CAS has
 3 APIs

=> d que 130

```

L9          3 SEA FILE=REGISTRY ABB=ON PLU=ON ("ANTIHEMOPHILIC C FACTOR"/CN
            OR "ANTIHEMOPHILIC FACTOR"/CN OR "ANTIHEMOPHILIC FACTOR A"/CN
            OR "ANTIHEMOPHILIC FACTOR B"/CN OR "ANTIHEMOPHILIC FACTOR
            C"/CN)
L17         4464 SEA FILE=HCAPLUS ABB=ON PLU=ON DENATURATION+PFT,NT/CT
L25         4656 SEA FILE=HCAPLUS ABB=ON PLU=ON L9 OR AHP/OBI
L29         5 SEA FILE=HCAPLUS ABB=ON PLU=ON L25 AND L17
L30         2 SEA FILE=HCAPLUS ABB=ON PLU=ON L29 AND (PARTICLES OR
            DISPERSION)/TI
  
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=> d que 137

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L9          3 SEA FILE=REGISTRY ABB=ON PLU=ON ("ANTIHEMOPHILIC C FACTOR"/CN
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            OR "ANTIHEMOPHILIC FACTOR B"/CN OR "ANTIHEMOPHILIC FACTOR
            C"/CN)
L13         194366 SEA FILE=HCAPLUS ABB=ON PLU=ON CONFORMATION+PFT,NT/CT
L19         73810 SEA FILE=HCAPLUS ABB=ON PLU=ON MOLECULAR ASSOCIATION+PFT/CT
L20         689 SEA FILE=HCAPLUS ABB=ON PLU=ON DENATURANTS+PFT/CT
L21         8228 SEA FILE=HCAPLUS ABB=ON PLU=ON STABILIZING AGENTS+PFT/CT
L22         16239 SEA FILE=HCAPLUS ABB=ON PLU=ON LIPOSOMES+PFT,NT/CT
L23         86371 SEA FILE=HCAPLUS ABB=ON PLU=ON DRUG DELIVERY SYSTEMS/CT
L24         7468 SEA FILE=HCAPLUS ABB=ON PLU=ON L23(L)LIPOSOM?
L25         4656 SEA FILE=HCAPLUS ABB=ON PLU=ON L9 OR AHP/OBI
L26         111 SEA FILE=HCAPLUS ABB=ON PLU=ON L25 AND L13
L32         89 SEA FILE=HCAPLUS ABB=ON PLU=ON L25 AND L19
L33         189 SEA FILE=HCAPLUS ABB=ON PLU=ON L26 OR L32
L34         1 SEA FILE=HCAPLUS ABB=ON PLU=ON L33 AND (L20 OR L21)
L35         1 SEA FILE=HCAPLUS ABB=ON PLU=ON L33 AND L22
L36         1 SEA FILE=HCAPLUS ABB=ON PLU=ON L33 AND L24
L37         2 SEA FILE=HCAPLUS ABB=ON PLU=ON (L34 OR L35 OR L36)
  
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=> d que 161

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L9          3 SEA FILE=REGISTRY ABB=ON PLU=ON ("ANTIHEMOPHILIC C FACTOR"/CN
            OR "ANTIHEMOPHILIC FACTOR"/CN OR "ANTIHEMOPHILIC FACTOR A"/CN
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L17         4464 SEA FILE=HCAPLUS ABB=ON PLU=ON DENATURATION+PFT,NT/CT
  
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| L23 | 86371 | SEA | FILE=HCAPLUS | ABB=ON | PLU=ON | DRUG DELIVERY SYSTEMS/CT |
| L24 | 7468 | SEA | FILE=HCAPLUS | ABB=ON | PLU=ON | L23(L)LIPOSOM? |
| L25 | 4656 | SEA | FILE=HCAPLUS | ABB=ON | PLU=ON | L9 OR AHP/OBI |
| L29 | 5 | SEA | FILE=HCAPLUS | ABB=ON | PLU=ON | L25 AND L17 |
| L30 | 2 | SEA | FILE=HCAPLUS | ABB=ON | PLU=ON | L29 AND (PARTICLES OR DISPERSION)/TI |
| L38 | 47 | SEA | FILE=HCAPLUS | ABB=ON | PLU=ON | L25 AND (L22 OR L24) |
| L39 | 2 | SEA | FILE=HCAPLUS | ABB=ON | PLU=ON | L38 AND DENATUR? |
| L40 | 2 | SEA | FILE=HCAPLUS | ABB=ON | PLU=ON | L38 AND FOLD? |
| L41 | 43 | SEA | FILE=HCAPLUS | ABB=ON | PLU=ON | L38 NOT (L39 OR L40) |
| L42 | 43 | SEA | FILE=HCAPLUS | ABB=ON | PLU=ON | L41 NOT L30 |
| L43 | 23315 | SEA | FILE=HCAPLUS | ABB=ON | PLU=ON | GENE THERAPY/CT |
| L44 | 32 | SEA | FILE=HCAPLUS | ABB=ON | PLU=ON | L42 NOT L43 |
| L61 | 8 | SEA | FILE=HCAPLUS | ABB=ON | PLU=ON | L44 AND (CONCENTRATED FACTOR IX OR POLYMERIZABLE OR CONTAINING COAGULATION OR IX CONCENTRATE OR BIOPOLYMERS OR FATTY OR INORGANIC)/TI |

=> s l30 or l37 or l61

L180 11 L30 OR L37 OR L61

11 cites from HCA PLUS

=> file medline

FILE 'MEDLINE' ENTERED AT 16:15:11 ON 23 OCT 2003

FILE LAST UPDATED: 22 OCT 2003 (20031022/UP). FILE COVERS 1958 TO DATE.

On April 13, 2003, MEDLINE was reloaded. See HELP RLOAD for details.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2003 vocabulary. See <http://www.nlm.nih.gov/mesh/changes2003.html> for a description on changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d que 181

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| L66 | 10407 | SEA | FILE=MEDLINE | ABB=ON | PLU=ON | FACTOR VIII+NT/CT |
| L67 | 856 | SEA | FILE=MEDLINE | ABB=ON | PLU=ON | AHP |
| L68 | 15284 | SEA | FILE=MEDLINE | ABB=ON | PLU=ON | PROTEIN DENATURATION/CT |
| L69 | 305 | SEA | FILE=MEDLINE | ABB=ON | PLU=ON | PROTEIN RENATURATION/CT |
| L70 | 13862 | SEA | FILE=MEDLINE | ABB=ON | PLU=ON | PROTEIN FOLDING/CT |
| L71 | 132985 | SEA | FILE=MEDLINE | ABB=ON | PLU=ON | PROTEIN CONFORMATION+NT/CT |
| L72 | 18865 | SEA | FILE=MEDLINE | ABB=ON | PLU=ON | SOLVENTS/CT |
| L74 | 13 | SEA | FILE=MEDLINE | ABB=ON | PLU=ON | (L66 OR L67) AND L68 |
| L75 | 1 | SEA | FILE=MEDLINE | ABB=ON | PLU=ON | (L66 OR L67) AND L69 |
| L76 | 10 | SEA | FILE=MEDLINE | ABB=ON | PLU=ON | (L66 OR L67) AND L70 |
| L77 | 175 | SEA | FILE=MEDLINE | ABB=ON | PLU=ON | (L66 OR L67) AND L71 |
| L78 | 3 | SEA | FILE=MEDLINE | ABB=ON | PLU=ON | (L74 OR L75 OR L76 OR L77) AND L72 |
| L80 | 2558 | SEA | FILE=MEDLINE | ABB=ON | PLU=ON | GUANIDINE/CT |
| L81 | 1 | SEA | FILE=MEDLINE | ABB=ON | PLU=ON | L78 AND L80 |

=> d que 190

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| L80 | 2558 | SEA | FILE=MEDLINE | ABB=ON | PLU=ON | GUANIDINE/CT |
| L82 | 62950 | SEA | FILE=MEDLINE | ABB=ON | PLU=ON | HEAT/CT |
| L83 | 203 | SEA | FILE=MEDLINE | ABB=ON | PLU=ON | L66 AND (L80 OR L82) |
| L90 | 1 | SEA | FILE=MEDLINE | ABB=ON | PLU=ON | L83 AND PHOSPHATIDYL? |

=> d que 1109

L66 10407 SEA FILE=MEDLINE ABB=ON PLU=ON FACTOR VIII+NT/CT
 L106 106151 SEA FILE=MEDLINE ABB=ON PLU=ON TEMPERATURE/CT
 L107 80 SEA FILE=MEDLINE ABB=ON PLU=ON L66 AND L106
 L109 1 SEA FILE=MEDLINE ABB=ON PLU=ON L107 AND (PHOSPHATIDYL? OR
 LIPOSOM?)

=> d que 1118

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 L106 106151 SEA FILE=MEDLINE ABB=ON PLU=ON TEMPERATURE/CT
 L111 3 SEA FILE=MEDLINE ABB=ON PLU=ON L66 AND DRUG CARRIER/CT
 L112 24834 SEA FILE=MEDLINE ABB=ON PLU=ON DRUG STABILITY/CT
 L113 59 SEA FILE=MEDLINE ABB=ON PLU=ON L112 AND L66
 L114 2423 SEA FILE=MEDLINE ABB=ON PLU=ON L66(L)(TU OR PK OR PD OR
 AE)/CT
 L115 11 SEA FILE=MEDLINE ABB=ON PLU=ON L113 AND L114
 L117 4 SEA FILE=MEDLINE ABB=ON PLU=ON (L111 OR L115) AND (L106 OR
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 L118 3 SEA FILE=MEDLINE ABB=ON PLU=ON L117 NOT ADMINISTRATION/TI

=> d que 1120

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 L111 3 SEA FILE=MEDLINE ABB=ON PLU=ON L66 AND DRUG CARRIER/CT
 L120 1 SEA FILE=MEDLINE ABB=ON PLU=ON L111 AND LIPOSOMES/TI

=> d que 1122

L66 10407 SEA FILE=MEDLINE ABB=ON PLU=ON FACTOR VIII+NT/CT
 L68 15284 SEA FILE=MEDLINE ABB=ON PLU=ON PROTEIN DENATURATION/CT
 L69 305 SEA FILE=MEDLINE ABB=ON PLU=ON PROTEIN RENATURATION/CT
 L70 13862 SEA FILE=MEDLINE ABB=ON PLU=ON PROTEIN FOLDING/CT
 L71 132985 SEA FILE=MEDLINE ABB=ON PLU=ON PROTEIN CONFORMATION+NT/CT
 L114 2423 SEA FILE=MEDLINE ABB=ON PLU=ON L66(L)(TU OR PK OR PD OR
 AE)/CT
 L121 15 SEA FILE=MEDLINE ABB=ON PLU=ON L114 AND (L68 OR L69 OR L70
 OR L71)
 L122 1 SEA FILE=MEDLINE ABB=ON PLU=ON L121 AND HEAT DENATURATION/TI

=> s 181 or 190 or 1109 or 1118 or 1120 or 1122

L181 8 L81 OR L90 OR L109 OR L118 OR L120 OR L122

8 cites from medline

=> file wpids

FILE 'WPIDS' ENTERED AT 16:15:15 ON 23 OCT 2003
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FILE LAST UPDATED: 22 OCT 2003 <20031022/UP>
 MOST RECENT DERWENT UPDATE: 200368 <200368/DW>
 DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> NEW WEEKLY SDI FREQUENCY AVAILABLE --> see NEWS <<<

>>> PATENT IMAGES AVAILABLE FOR PRINT AND DISPLAY <<<

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http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
<http://thomsonderwent.com/coverage/latestupdates/> <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
 GUIDES, PLEASE VISIT:
<http://thomsonderwent.com/support/userguides/> <<<

=> d que 1179

L163 1062 SEA FILE=WPIDS ABB=ON PLU=ON FACTOR VIII? OR AHP OR AHF OR
 ANTIHEMOPHILIC(W) (FACTOR OR PROTEIN) OR ANTIHAEMOPHILIC(W)
 (FACTOR OR PROTEIN)

L164 20 SEA FILE=WPIDS ABB=ON PLU=ON L163 AND LIPOSOM?
 L179 2 SEA FILE=WPIDS ABB=ON PLU=ON L164 AND (COMPLEXING OR
 DIELECTRIC)/TI

2 cites from
 WPI

=> dup rem 1181 1180 1179 removing duplicate
 FILE 'MEDLINE' ENTERED AT 16:15:52 ON 23 OCT 2003 cites

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 PROCESSING COMPLETED FOR L180
 PROCESSING COMPLETED FOR L179

L182 20 DUP REM L181 L180 L179 (1 DUPLICATE REMOVED)
 ANSWERS '1-8' FROM FILE MEDLINE
 ANSWERS '9-19' FROM FILE HCAPLUS
 ANSWER '20' FROM FILE WPIDS

20 cites total

=> d ibib abs ind 1-8

ind = indexing terms - all of the topics
 covered in the full paper
 are listed in the indexing.

L182 ANSWER 1 OF 20 MEDLINE on STN
 ACCESSION NUMBER: 2001118088 MEDLINE
 DOCUMENT NUMBER: 20582623 PubMed ID: 11148054
 TITLE: Conformational origin of the aggregation of recombinant
 human factor VIII.
 AUTHOR: Grillo A O; Edwards K L; Kashi R S; Shipley K M; Hu L;
 Besman M J; Middaugh C R
 CORPORATE SOURCE: Department of Pharmaceutical Chemistry, University of
 Kansas, Lawrence, Kansas 66046 and Hyland Immuno Division,
 Baxter Healthcare Corporation, Duarte, California 91010,
 USA.
 SOURCE: BIOCHEMISTRY, (2001 Jan 16) 40 (2) 586-95.
 Journal code: 0370623. ISSN: 0006-2960.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200102
 ENTRY DATE: Entered STN: 20010322
 Last Updated on STN: 20010322
 Entered Medline: 20010215

The indexing
 can have
 information
 not covered in
 the abstract.

AB Aggregation of proteins is a major problem in their use as drugs and is
 also involved in a variety of pathological diseases. In this study,
 biophysical techniques were employed to investigate aggregate formation in
 the pharmaceutically important protein, recombinant human factor VIII
 (rhFVIII). Recombinant human factor VIII incubated in solution at 37
 degrees C formed soluble aggregates as detected by molecular sieve
 chromatography and dynamic light scattering. This resulted in a
 corresponding loss of biological activity. Fluorescence and CD spectra of

the thermally stressed rhFVIII samples did not, however, suggest significant differences in protein conformation. To identify conformational changes in rhFVIII that may be involved in rhFVIII aggregation, temperature and solutes were used to perturb the native structure of rhFVIII. Far-UV CD and FTIR studies of rhFVIII as a function of temperature revealed conformational changes corresponding to an increase in intermolecular beta-sheet content beginning at approximately 45 degrees C with significant aggregation observed above 60 degrees C. Fluorescence and DSC studies of rhFVIII also indicated conformational changes initiating between 45 and 50 degrees C. An increase in the exposure of hydrophobic surfaces was observed beginning at approximately 40 degrees C, as monitored by increased binding of the fluorescent probe, bis-anilinonaphthalene sulfonic acid (bis-ANS). Perturbation by various solutes produced several transitions prior to extensive unfolding of rhFVIII. In all cases, a common transition, characterized by an increase in the wavelength of the fluorescence emission maximum of rhFVIII from approximately 330 to 335 nm, was observed during thermal and solute perturbation of factor VIII. Moreover, this transition was correlated with an increased association of factor VIII upon incubation at 37 degrees C in the presence of various solutes. These results suggest that association of rhFVIII in solution was initiated by a small transition in the tertiary structure of the protein which produced a nucleating species that led to the formation of inactive soluble aggregates.

CT Check Tags: Human; Support, Non-U.S. Gov't

1-Propanol

Body Temperature

Calorimetry, Differential Scanning

Chromatography, Gel

Circular Dichroism

*Factor VIII: CH, chemistry

Factor VIII: GE, genetics

Factor VIII: ME, metabolism

Guanidine

Heat

Light

Protein Conformation

Protein Folding

Protein Structure, Secondary

Protein Structure, Tertiary

*Recombinant Proteins: CH, chemistry

Recombinant Proteins: ME, metabolism

Scattering, Radiation

Solvents

Spectrometry, Fluorescence

Urea

RN 113-00-8 (Guanidine); 57-13-6 (Urea); 71-23-8 (1-Propanol); 9001-27-8 (Factor VIII)

CN 0 (Recombinant Proteins); 0 (Solvents)

L182 ANSWER 2 OF 20

MEDLINE on STN

ACCESSION NUMBER: 1998115143 MEDLINE

DOCUMENT NUMBER: 98115143 PubMed ID: 9453053

TITLE: Recombinant factor VIII SQ--inactivation kinetics in aqueous solution and the influence of disaccharides and sugar alcohols.

AUTHOR: Fatouros A; Osterberg T; Mikaelsson M

CORPORATE SOURCE: Department of Pharmaceutical Technology, Pharmacia & Upjohn AB, Stockholm, Sweden.. angelica.fatouros@eu.pnu.com

SOURCE: PHARMACEUTICAL RESEARCH, (1997 Dec) 14 (12) 1679-84.

Journal code: 8406521. ISSN: 0724-8741.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199804

ENTRY DATE: Entered STN: 19980416

Last Updated on STN: 19980416

Entered Medline: 19980406

AB PURPOSE: To investigate the influence of various nonreducing disaccharides and sugar alcohols on the inactivation kinetics of recombinant factor VIII SQ (r-VIII SQ) in aqueous solution not containing albumin as a stabiliser. METHODS: The stability of r-VIII SQ was followed using measurement of activity (VIII:C) and HPLC gel filtration at different temperatures. The thermal stability was investigated using differential scanning calorimetry (DSC). RESULTS: The decline in VIII:C followed pseudo-first order kinetics. However, the Arrhenius plot was not linear for formulations without carbohydrate, demonstrating a distinct, reproducible curvature. The reaction rate at 5 degrees C was faster than expected from the Arrhenius kinetics. The energy of activation (Ea) for formulations without added carbohydrates, derived from the linear part of the Arrhenius plot, varied between 77 and 86 kJ/mole in the temperature range 20-37 degrees C. The addition of 600 mg/ml sucrose increased the Ea to 104 kJ/mole. DSC measurements showed that Tm' was 64.2 +/- 0.2 degrees C for r-VIII SQ without stabiliser. This value increased linearly with increasing concentrations of carbohydrate. This stabilising effect is most probably explained by the theory of preferential hydration. CONCLUSIONS: The inactivation kinetics of r-VIII SQ in aqueous solution without addition of carbohydrates followed pseudo-first order kinetics but the Arrhenius plot was nonlinear. Sucrose and sorbitol both had highly stabilising effects on r-VIII SQ at concentrations above 300 mg/ml. The preparation containing 600 mg/ml sucrose was stable for at least 12 months at 5 degrees C and 6 months at 25 degrees C.

CT Check Tags: Animal; Male
Calorimetry, Differential Scanning
*Disaccharides: CH, chemistry
Drug Stability
Drug Tolerance
Factor VIII: BI, biosynthesis
*Factor VIII: CH, chemistry
Factor VIII: PD, pharmacology
Kinetics
Rabbits
Recombinant Proteins: CH, chemistry
Solutions
*Sugar Alcohols: CH, chemistry
Temperature

RN 9001-27-8 (Factor VIII)

CN 0 (Disaccharides); 0 (Recombinant Proteins); 0 (Solutions); 0 (Sugar Alcohols)

L182 ANSWER 3 OF 20 MEDLINE on STN
ACCESSION NUMBER: 94235710 MEDLINE
DOCUMENT NUMBER: 94235710 PubMed ID: 8180259
TITLE: Stability of factor VIII preparation in continuous infusion.
AUTHOR: Martinowitz U
CORPORATE SOURCE: National Hemophilia Center, Sheba Medical Center, Tel-Hashomer, Israel.
SOURCE: ANNALS OF HEMATOLOGY, (1994) 68 Suppl 3 S69-71. Journal code: 9107334. ISSN: 0939-5555.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199406
ENTRY DATE: Entered STN: 19940621
Last Updated on STN: 19990129
Entered Medline: 19940614

CT Check Tags: Comparative Study; Human
Drug Stability
*Factor VIII: AD, administration & dosage
*Factor VIII: CH, chemistry
Factor VIII: TU, therapeutic use
Glass

*Hemophilia A: ME, metabolism
 Infusions, Intravenous
 Kinetics
 Plastics
 Temperature
 Time Factors

RN 9001-27-8 (Factor VIII)
 CN 0 (Glass); 0 (Plastics)

L182 ANSWER 4 OF 20 MEDLINE on STN
 ACCESSION NUMBER: 93232040 MEDLINE
 DOCUMENT NUMBER: 93232040 PubMed ID: 8473326
 TITLE: Membrane binding kinetics of factor VIII indicate a complex binding process.
 AUTHOR: Bardelle C; Furie B; Furie B C; Gilbert G E
 CORPORATE SOURCE: Center for Hemostasis and Thrombosis Research, New England Medical Center, Boston, Massachusetts.
 CONTRACT NUMBER: HL42443 (NHLBI)
 SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1993 Apr 25) 268 (12) 8815-24.
 Journal code: 2985121R. ISSN: 0021-9258.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199305
 ENTRY DATE: Entered STN: 19930604
 Last Updated on STN: 19970203
 Entered Medline: 19930514

AB Factor VIII functions as a component of the tenase enzyme complex upon phospholipid membranes. Factor VIII binds to **phosphatidylserine**-containing membranes and apparently provides high affinity binding sites for factor IXa upon these membranes. We have characterized the binding kinetics of human factor VIII with **phosphatidylserine**-containing membranes and directly compared the measured properties with those of factor V. The initial phase of association was evaluated in a stopped-flow apparatus by fluorescence energy transfer from aromatic residues in the protein to dansyl-labeled **phosphatidylethanolamine** in the vesicles. Association proceeded at an apparent second-order rate of 0.12 microM⁻¹ s⁻¹ for extruded phospholipid vesicles and 0.42 microM⁻¹ s⁻¹ for sonicated vesicles under pseudo-first-order conditions in which the phospholipid concentration determined the rate. Increased temperature resulted in more rapid association, and the effect decreased in the order extruded vesicles > sonicated vesicles > extruded vesicles of dioleoylphospholipids, indicating that the structure of the phospholipid membrane contributes to the activation energy of binding. The binding of fluorescein-labeled factor VIII to membranes supported on glass microspheres (lipospheres) was monitored by flow cytometry. Under conditions in which the factor VIII concentration determined the rate there was rapid initial association at 6.9 microM⁻¹ s⁻¹, accounting for half of the bound factor VIII, and a slower component of 0.87 microM⁻¹ s⁻¹, accounting for the other half. Likewise, the dissociation of factor VIII from liposphere membranes was biphasic with a faster component of 0.010 s⁻¹ and a slower component of 0.0012 s⁻¹. Rates of association and dissociation for factor V were similar to those for factor VIII and were biphasic. These results allow estimation of the size of the phospholipid sites that interact with factors VIII and V and suggest that both proteins bind to membranes via a multistep process in which rapid association is followed by a slower step yielding higher affinity binding.

CT Check Tags: Animal; Human; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
 Cattle
 *Factor VIII: ME, metabolism
 Kinetics
 *Membranes, Artificial
 Phosphatidylethanolamines: ME, metabolism
 Temperature

RN 9001-27-8 (Factor VIII)
 CN 0 (Phosphatidylethanolamines)

L182 ANSWER 5 OF 20 MEDLINE on STN
 ACCESSION NUMBER: 89389312 MEDLINE
 DOCUMENT NUMBER: 89389312 PubMed ID: 2506696
 TITLE: Severely heated therapeutic factor VIII concentrate of high specific activity.
 AUTHOR: Winkelman L; Owen N E; Evans D R; Evans H; Haddon M E; Smith J K; Prince P J; Williams J D; Lane R S
 CORPORATE SOURCE: Plasma Fractionation Laboratory, Churchill Hospital, Oxford, UK.
 SOURCE: VOX SANGUINIS, (1989) 57 (2) 97-103.
 Journal code: 0413606. ISSN: 0042-9007.
 PUB. COUNTRY: Switzerland
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 198910
 ENTRY DATE: Entered STN: 19900309
 Last Updated on STN: 19900309
 Entered Medline: 19891025

AB A new method for the manufacture of a heated factor VIII concentrate of high specific activity (2-6 IU factor VIII:C/mg protein) has been developed. Addition of heparin to cryoprecipitate extract at acid pH precipitated fibrinogen and fibronectin. Factor VIII was then recovered from the supernatant by precipitation with glycine and sodium chloride. After re-solution and desalting on Sephadex G-25, the concentrate was sterile-filtered and lyophilised. The dried product was stable to heating in the final container at 80 degrees C for 72 h. Data from 25 consecutive batches of concentrate prepared from 1,200-1,500 kg plasma pools are presented. The mean final yield of heated product was 190 IU factor VIII:C/kg plasma. The concentrate has been found to be safe and effective in clinical use.

CT Check Tags: Human
 Drug Stability
 Factor VIII: AD, administration & dosage
 Factor VIII: AE, adverse effects
 *Factor VIII: IP, isolation & purification
 Freezing
 Glycine
 Heat
 Heparin
 Precipitation
 Salts: IP, isolation & purification
 Sodium Chloride

RN 56-40-6 (Glycine); 7647-14-5 (Sodium Chloride); 9001-27-8 (Factor VIII);
 9005-49-6 (Heparin)
 CN 0 (Salts)

L182 ANSWER 6 OF 20 MEDLINE on STN
 ACCESSION NUMBER: 88018701 MEDLINE
 DOCUMENT NUMBER: 88018701 PubMed ID: 3116715
 TITLE: The influence of pH on heat denaturation of anti-haemophilic cryoprecipitate.
 AUTHOR: Skjonsberg O H; Gravem K; Kierulf P; Vaeret A; Godal H C
 CORPORATE SOURCE: Ulleval Hospital, University Clinic, Oslo, Norway.
 SOURCE: THROMBOSIS RESEARCH, (1987 Jul 15) 47 (2) 183-90.
 Journal code: 0326377. ISSN: 0049-3848.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 198710
 ENTRY DATE: Entered STN: 19900305
 Last Updated on STN: 19900305
 Entered Medline: 19871028

AB The influence of pH on heat denaturation of anti-haemophilic cryoprecipitate (CP) was studied by using phosphate and citrate buffers at three different pH levels for processing lyophilized, heat treated CP. The solubility and the content of FVIII:C and fibrinogen were determined following heating at 68 degrees C for 24 hours and compared to "ordinary", non-heated CP. Both the solubility and the biological activity were best preserved in the most acidic samples (pH 5.7-6.7), these batches equalled non-heated CP. At higher pH, heat treatment resulted in reduced solubility and a more pronounced loss of FVIII:C and fibrinogen. Amino acids (Syntamin 17) have previously been shown to stabilize CP during heat treatment. Some of the stabilizing effect seems to be due to a large buffering capacity, maintaining a low pH during lyophilization and heating. Raising the pH level in Syntamin-CP from 6.6 to 7.8 resulted in decreased solubility and FVIII:C content. The quality of heat treated, acidic Syntamin-CP was comparable to that of heated, acidic phosphate- and citrate-CP. We conclude that buffers used for processing heat treated CP should be of low pH, and that acidic buffers may replace Syntamin without lowering the quality of the heated product.

CT Check Tags: Human
 Amino Acids: PD, pharmacology
 *Blood Preservation: MT, methods
 Buffers
 Citrates: PD, pharmacology
 *Factor VIII: AN, analysis
 Factor VIII: TU, therapeutic use
 Freeze Drying
 Freezing
 Heat
 *Hydrogen-Ion Concentration
 Phosphates: PD, pharmacology
 Protein Denaturation: DE, drug effects
 Solubility

RN 65072-01-7 (Travasol); 9001-27-8 (Factor VIII)
 CN 0 (Amino Acids); 0 (Buffers); 0 (Citrates); 0 (Phosphates)

L182 ANSWER 7 OF 20 MEDLINE on STN
 ACCESSION NUMBER: 89258028 MEDLINE
 DOCUMENT NUMBER: 89258028 PubMed ID: 6443849
 TITLE: Preparation of liposomes containing factor VIII
 for oral treatment of haemophilia.
 AUTHOR: Kirby C J; Gregoriadis G
 CORPORATE SOURCE: Division of Clinical Sciences, Clinical Research Centre,
 Harrow, Middlesex, England.
 SOURCE: JOURNAL OF MICROENCAPSULATION, (1984 Jan-Mar) 1 (1) 33-45.
 Journal code: 8500513. ISSN: 0265-2048.
 PUB. COUNTRY: ENGLAND: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 198906
 ENTRY DATE: Entered STN: 19900306
 Last Updated on STN: 19990129
 Entered Medline: 19890627

AB Different types of liposomes composed of a variety of lipids have been compared for their ability to incorporate Factor VIII, with a view to attempting oral therapy of haemophilia. Reverse evaporation liposomes (REV) composed of unsaturated phospholipids, allowed adequate levels of entrapment for administration to haemophilic dogs, but failed to promote entry of Factor VIII into the vasculature, possibly due to liposome breakdown and denaturation of Factor VIII within the gastrointestinal tract. A novel technique was therefore developed which made possible high-yield entrapment of Factor VIII in much more stable liposomes based on the saturated phospholipid, distearoyl phosphatidylcholine. This new technique has a number of other important features which make it an attractive method for the incorporation of a wide range of materials into liposomes.

CT Check Tags: Animal

Administration, Oral
Dogs

Drug Carriers

*Drug Compounding: MT, methods

*Factor VIII: AD, administration & dosage

Factor VIII: TU, therapeutic use

*Hemophilia A: DT, drug therapy

Liposomes

Phosphatidylcholines

RN 4539-70-2 (1,2-distearoyllecithin); 9001-27-8 (Factor VIII)

CN 0 (Drug Carriers); 0 (Liposomes); 0 (Phosphatidylcholines)

L182 ANSWER 8 OF 20

MEDLINE on STN

ACCESSION NUMBER: 83283329 MEDLINE

DOCUMENT NUMBER: 83283329 PubMed ID: 6411112

TITLE: The interaction between factor VIII clotting antigen (VIIIICAg) and phospholipid.

AUTHOR: Yoshioka A; Peake I R; Furlong B L; Furlong R A; Giddings J C; Bloom A L

SOURCE: BRITISH JOURNAL OF HAEMATOLOGY, (1983 Sep) 55 (1) 27-36.
Journal code: 0372544. ISSN: 0007-1048.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 198310

ENTRY DATE: Entered STN: 19900319

Last Updated on STN: 19900319

Entered Medline: 19831008

AB The interaction between factor VIII clotting antigen (VIIIICAg) and phospholipid (PL) was studied using a two-site solid phase immunoradiometric assay (IRMA) for VIII CAg. Incubation (2 h, 37 degrees C) of normal plasma, cryoprecipitate or factor VIII concentrate with Diagen PL (0.5 mg/unit VIIIICAg) resulted in 80-90% loss of IRMA-measurable VIIIICAg. No loss of factor VIII related antigen (VIIIIRAg) or factor VIII clotting activity (VIIIIC) was seen. Treatment of factor VIII concentrate with purified PLs showed greatest VIIIICAg reduction with **phosphatidylserine**, less with **phosphatidylethanolamine**, and very little with **phosphatidylcholine**. The action of phospholipase-C (PL-C) on VIIIICAg-PL complexes was investigated, with enzyme activity being monitored by thin-layer chromatography. Treatment of normal plasma, cryoprecipitate or factor VIII concentrate with PL-C (5 u/unit VIIIICAg) resulted in 25%, 25% and 30% increases in VIIIICAg. No increase in VIIIIC or VIIIIRAg was seen. Preincubation of factor VIII concentrate with PL, followed by PL-C incubation, resulted in 70-80% recovery of measurable VIIIICAg. Incubation of 'activated' prothrombin complex with PL-C increased VIIIICAg by 44% (Autoplex) and 80% (FEIBA), indicating VIIIICAg-PL complexes are present. Incubation of factor VIII concentrate with fresh platelet lysate led to a reduction in VIIIICAg (100 u/dl to 21 u/dl). In fresh platelet lysate alone low VIIIICAg levels were detectable (0.71×10^{-3} u/10⁹ plt). After PL-C incubation VIIIICAg levels increased to 9.8×10^{-3} u/10⁹ plt (14-fold increase). Thus VIIIICAg in platelets may be hidden by VIIIICAg-PL complexes.

CT Check Tags: Human

*Antigens: ME, metabolism

Blood Platelets: ME, metabolism

Cell Extracts

Factor IX: ME, metabolism

Factor IXa

*Factor VIII: IM, immunology

Factor VIII: ME, metabolism

Heat

Phospholipase C: PD, pharmacology

*Phospholipids: BL, blood

Radioimmunoassay

RN 9001-27-8 (Factor VIII); 9001-28-9 (Factor IX)

CN 0 (Antigens); 0 (Cell Extracts); 0 (Phospholipids); EC 3.1.4.3

(Phospholipase C); EC 3.4.21.22 (Factor IXa)

=> d ibib abs hitrn 9

L182 ANSWER 9 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 1
 ACCESSION NUMBER: 2002:428652 HCAPLUS
 DOCUMENT NUMBER: 137:10979
 TITLE: Preparation of antihemophilic factor A-associated
dispersion system
 INVENTOR(S): Balasubramanian, Sathyamangalam V.; Besman, Marc;
 Kashi, Ramesh; Ramani, Karthik
 PATENT ASSIGNEE(S): The Research Foundation of State University of New
 York, USA; Baxter Healthcare Corporation
 SOURCE: PCT Int. Appl., 40 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-------------------|----------|
| WO 2002043665 | A2 | 20020606 | WO 2001-US48201 | 20011130 |
| WO 2002043665 | A3 | 20020711 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2002030607 | A5 | 20020611 | AU 2002-39607 | 20011130 |
| US 2002132982 | A1 | 20020919 | US 2001-997936 | 20011130 |
| PRIORITY APPLN. INFO.: | | | | |
| | | | US 2000-250137P P | 20001130 |
| | | | WO 2001-US48201 W | 20011130 |
| AB A method for complexing AHF (antihemophilic factor A) in a dispersed medium, includes: providing an AHF protein, altering the conformational state of the AHF protein to expose hydrophobic domains therein, binding a stabilizer to the exposed hydrophobic domains, and at least partially reversing the alteration to assoc. at least a portion of the protein with the stabilizer. A stabilized AHF dosage form, wherein >25% of the AHF mol., is assocd. with a stabilizer is also disclosed. DMPC, brain phosphatidylserines, and cholesterol were dissolved in chloroform and the solvent was removed. The multilamellar vesicles thus formed were filtered through a polycarbonate filter to form small unilamellar (SUVs) below 200 nm. The liposomes encapsulating the protein were formed by mixing the liposomes in protein (AHF) contg. buffer and ethanol followed by gentle swirling .gtoreq.37.degree. to generate intermediate structures. The PEGylation of these particles were performed by adding DSPE-PEG. | | | | |
| IT 113189-02-9, Blood coagulation factor VIII RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (prepn. of antihemophilic factor A-assocd. dispersion system) | | | | |

=> d ibib abs hitrn 10

L182 ANSWER 10 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 2003:300859 HCAPLUS
 DOCUMENT NUMBER: 138:309313
 TITLE: Pro-micelle pharmaceutical compositions containing
fatty esters
 INVENTOR(S): Cho, Young W.; Lee, Keith Kwang-Ho
 PATENT ASSIGNEE(S): IMI Biomed, Inc., USA

SOURCE: PCT Int. Appl., 27 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2003030865 | A1 | 20030417 | WO 2002-US28159 | 20020905 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |

US 2003078194 A1 20030424 US 2001-974942 20011011

PRIORITY APPLN. INFO.: US 2001-974942 A 20011011

AB The present invention provides pro-micelle compns. comprising a pharmaceutical encapsulated with a membrane of esterified C12-18 fatty acids. In the mammalian intestine, exposure to C12-18 fatty acids results in conversion of the pro-micelle to a stable micelle that effectively delivers the pharmaceutical to the systemic circulation. The present invention further provides methods of making and using such compns. A liq. orally administrable insulin-contg. formulation was prepd. as follows: Sub-mixt.-A is prepd. by dissolving the following ingredients in 95% ethanol; glycerol monooleate 2.8-3.2, lecithin 3.0-3.5, cholesterol 2.8-4.6, phosphatidic acid 0.15-0.33, and lysophosphatidylcholine 3.2-9.8 g; an antioxidant soln. was prepd. contg. Pr gallate 10-18, BHA 8-14, BHT 10-20; Sub-mixt. B was prepd. by dissolving the following ingredients in 95% EtOH; PEG-40 stearate 1.5-3.9, oleic acid, 36.5-48.9, and .alpha.-tocopherol 2.0-3.9 g, propylparaben 92-118, ascorbic acid 92-121, antioxidant 200-340, and methylparaben 580-720 mg. Sub-mixt. contained insulin (250 mg) and aprotinin, N-acetylneuraminic acid 0.9-1.8, cyclohexylurea 0.05 mg. All the above mixts. were combined and gave a microemulsion.

IT 9001-28-9, Blood coagulation factor IX 113189-02-9, Blood coagulation factor VIII

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (pro-micelle pharmaceutical compns. contg. fatty esters)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ind 10

L182 ANSWER 10 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN

IC ICM A61K009-127

ICS A61K009-64; A61K009-16; A61K038-28; C07K016-00

CC 63-6 (Pharmaceuticals)

Section cross-reference(s): 1, 2

ST promicelle pharmaceutical insulin fatty ester

IT Drug delivery systems

(capsules; lpro-micelle pharmaceutical compns. contg. fatty esters)

IT Fatty acids, biological studies

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(esters, C12-18; pro-micelle pharmaceutical compns. contg. fatty esters)

IT Drug delivery systems

(liposomes; pro-micelle pharmaceutical compns. contg. fatty esters)

IT Drug delivery systems

(liqs., oral; pro-micelle pharmaceutical compns. contg. fatty esters)

- IT Drug delivery systems
(microemulsions; pro-micelle pharmaceutical compns. contg. fatty esters)
- IT Antidiabetic agents
Drug delivery systems
Human
Surfactants
(pro-micelle pharmaceutical compns. contg. fatty esters)
- IT Fatty acids, biological studies
Gelatin, biological studies
Lecithins
Lysophosphatidylcholines
Phosphatidic acids
Phospholipids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pro-micelle pharmaceutical compns. contg. fatty esters)
- IT 9004-10-8, Insulin, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pro-micelle pharmaceutical compns. contg. fatty esters)
- IT 50-18-0, Cyclophosphamide 53-86-1, Indomethacin 54-05-7, ChloroQuine 57-22-7, Vincristine 57-47-6, Physostigmine 57-88-5, Cholesterol, biological studies 59-02-9, D-.alpha.-Tocopherol 90-34-6, PrimaQuine 129-20-4, Oxyphenbutazone 130-95-0, Quinine 147-52-4, Nafcillin 525-66-6, Propranolol 533-45-9 563-24-6, Glycerophosphatidylcholine 1403-66-3, Gentamicin 9001-28-9, Blood coagulation factor IX 9002-72-6, Growth hormone 9007-12-9, Calcitonin 9039-53-6, Urokinase 10238-21-8, Glyburide 11096-26-7, Erythropoietin 23214-92-8, Doxorubicin 25953-19-9, Cephazolin 36322-90-4, Feldene 54910-89-3, Fluoxetine 113189-02-9, Blood coagulation factor VIII
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pro-micelle pharmaceutical compns. contg. fatty esters)

=> d ibib abs hitrn ind 11-19

L182 ANSWER 11 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2003:785259 HCAPLUS
TITLE: Inorganic-polymer complexes for the controlled release of compounds including medicinals
INVENTOR(S): Royer, Garfield P.
PATENT ASSIGNEE(S): Royer Biomedical, Inc., USA
SOURCE: U.S., 11 pp., Cont.-in-part of U.S. Ser. No. 935,300.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|-------------|
| US 6630486 | B1 | 20031007 | US 2000-509016 | 20000321 |
| US 6391336 | B1 | 20020521 | US 1997-935300 | 19970922 |
| WO 9915150 | A1 | 19990401 | WO 1998-US19528 | 19980922 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2003170307 | A1 | 20030911 | US 2003-365419 | 20030213 |
| PRIORITY APPLN. INFO.: | | | | |
| | | | US 1997-935300 | A2 19970922 |
| | | | WO 1998-US19528 | W 19980922 |
| | | | US 2000-509016 | A3 20000321 |

AB This invention relates generally to the prodn. and use of inorg.-polymer

complexes for the controlled release of compds. including medicinals.
 Advantageously, the inorg. used is calcium sulfate.

IT 113189-02-9, Factor VIII
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (inorg.-polymer complexes for controlled release of compds. including medicinals)

IC ICM A61K009-22
 ICS A61K009-16

NCL 514303000; 514777000; 514947000; 424468000; 424499000; 424422000;
 424423000; 424425000; 424426000; 424451000

CC 63-6 (Pharmaceuticals)
 Section cross-reference(s): 1, 2, 15

ST inorg polymer complex calcium sulfate hemihydrate controlled release drug;
 sustained release formulation inorg polymer complex calcium sulfate

IT Amino acids
 RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (cationic, polymers; inorg.-polymer complexes for controlled release of compds. including medicinals)

IT Peptides
 RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (cationic; inorg.-polymer complexes for controlled release of compds. including medicinals)

IT Drug delivery systems
 (controlled-release; inorg.-polymer complexes for controlled release of compds. including medicinals)

IT Albumins
 RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (defatted; inorg.-polymer complexes for controlled release of compds. including medicinals)

IT Toxoids
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (diphtheria; inorg.-polymer complexes for controlled release of compds. including medicinals)

IT Drug delivery systems
 (granules; inorg.-polymer complexes for controlled release of compds. including medicinals)

IT Drug delivery systems
 (injections, s.c.; inorg.-polymer complexes for controlled release of compds. including medicinals)

IT Analgesics
 Anesthetics
 Anti-inflammatory agents
 Antibacterial agents
 Antibiotics
 Antidepressants
 Antihypertensives
 Antitumor agents
 Cardiovascular agents
 Complexing agents
 Cylinders
 Liposomes
 Mammalia
 Surfactants
 Tranquilizers
 Vaccines
 (inorg.-polymer complexes for controlled release of compds. including medicinals)

IT Ethers
 Glycosaminoglycans
 Lecithins
 Lipids
 Polynucleotides
 Proteins
 RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL

- (Biological study); USES (Uses)
(inorg.-polymer complexes for controlled release of compds. including
medicinals)
- IT Cytokines
Enkephalins
Hormones, animal
Interferons
Interleukin 2
Interleukin 4
Interleukin 6
Opioids
Tumor necrosis factors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inorg.-polymer complexes for controlled release of compds. including
medicinals)
- IT **Drug delivery systems**
(liposomes; inorg.-polymer complexes for controlled release
of compds. including medicinals)
- IT Polymers
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(matrix; inorg.-polymer complexes for controlled release of compds.
including medicinals)
- IT Drug delivery systems
(polymer-bound; inorg.-polymer complexes for controlled release of
compds. including medicinals)
- IT Drug delivery systems
(prodrugs; inorg.-polymer complexes for controlled release of compds.
including medicinals)
- IT Drug delivery systems
(spheres; inorg.-polymer complexes for controlled release of compds.
including medicinals)
- IT Drug delivery systems
(sustained-release; inorg.-polymer complexes for controlled release of
compds. including medicinals)
- IT Drug delivery systems
(tablets; inorg.-polymer complexes for controlled release of compds.
including medicinals)
- IT Toxoids
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tetanus; inorg.-polymer complexes for controlled release of compds.
including medicinals)
- IT Drug delivery systems
(wafers; inorg.-polymer complexes for controlled release of compds.
including medicinals)
- IT 9012-33-3, hexosaminidase A
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(A; inorg.-polymer complexes for controlled release of compds.
including medicinals)
- IT 37377-93-8, .beta.-lipotropin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fragment; inorg.-polymer complexes for controlled release of compds.
including medicinals)
- IT 9004-34-6, Cellulose 9005-25-8, Starch 11138-66-2, Xanthan
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(inorg.-polymer complexes for controlled release of compds. including
medicinals)
- IT 57-88-5, cholesterol 59-46-1, procaine 140-28-3, benzathine
1406-11-7, polymyxin 7778-18-9, calcium sulfate 9002-98-6 9003-01-4,
polyacrylic acid 9003-47-8, polyvinylpyridine 9004-54-0, dextran
9004-61-9, hyaluronic acid 9005-32-7, alginic acid 9007-28-7,
chondroitin sulfate 9042-14-2, dextran sulfate 10034-76-1, calcium
sulfate hemihydrate 12619-70-4, cyclodextrin 22199-08-2, silver
sulfadiazine 24991-23-9 25322-68-3D, alcs., esters, or ethers
25513-46-6, polyglutamic acid 25608-40-6, polyaspartic acid
26063-13-8, polyaspartic acid 26336-38-9, polyvinylamine 26913-06-4,

Poly[imino(1,2-ethanediyl)]

RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(inorg.-polymer complexes for controlled release of compds. including medicinals)

IT 50-56-6, oxytocin 58-82-2, bradykinin 137-58-6, lidocaine 9001-27-8, Factor VIII 9002-01-1, streptokinase 9002-60-2, ACTH 9002-67-9, luteinizing hormone 9002-72-6, growth hormone 9002-76-0, gastrin 9002-79-3, melanocyte stimulating hormone 9007-92-5, glucagon 9034-39-3, growth hormone releasing factor 9034-40-6, LRH 9034-50-8, vasotocin 9061-61-4, nerve growth factor 11000-17-2, vasopressin 11096-26-7, erythropoietin 11128-99-7, Angiotensin II 33507-63-0, substance P 37228-64-1, glucocerebrosidase 39379-15-2, neurotensin 60118-07-2, endorphin 62229-50-9, epidermal growth factor 62683-29-8, Colony stimulating factor 64221-86-9, imipenem 74913-18-1, dynorphin 81627-83-0, M-CSF 83869-56-1, GM-CSF 85637-73-6, atrial natriuretic peptide 105857-23-6, Plasminogen activator (human tissue-type protein moiety) 109319-16-6, Factor VIII 113189-02-9, Factor VIII 143011-72-7, G-CSF

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(inorg.-polymer complexes for controlled release of compds. including medicinals)

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L182 ANSWER 12 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2000:344044 HCAPLUS

DOCUMENT NUMBER: 132:352804

TITLE: Method for preparation of vesicles loaded with biological structures, biopolymers and/or oligomers

INVENTOR(S): Barenholz, Yechezkel; Bar, Lilianne K.; Diminsky, Dvorah; Baru, Moshe

PATENT ASSIGNEE(S): Israel

SOURCE: U.S., 11 pp.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|-----------------|----------|
| US 6066331 | A | 20000523 | US 1996-710576 | 19960813 |
| PRIORITY APPLN. INFO.: | | | US 1996-710576 | 19960813 |

AB A compn. useful for prepg. vesicles loaded with biol. cell-structures, biopolymers and/or -oligomers is prepd. by solubilizing amphipathic material such as a phospholipid in a polar-protic solvent miscible with water, solubilizing biol. cell-structures, biopolymers and/or -oligomers in an aq. medium, mixing the polar-protic solvent contg. the amphipathic material with the aq. medium contg. the biol. cell-structures, biopolymers and/or -oligomers, and lyophilizing the resultant mixt. to form a dry product. The dry product is hydrated in an aq. medium to form the loaded vesicles. The polar-protic solvent may be tert-butanol, and the aq. medium may contain a salt such as sodium chloride, an isoosmotic cryoprotectant such as lactose, sucrose or trehalose, or a mixt. of the salt and the cryoprotectant. A medicament for disease treatment is formed by mixing the loaded vesicles with a pharmaceutically acceptable vehicle. A mixt. of DMPC-DMPG in a molar ratio of 9:1 resp. was prepd. in tert.-butanol. An aq. HBsAg soln. such as 0.9% NaCl in a 1:1 ratio was added. The final HBsAg: phospholipids (wt./wt.) ratio was 0.0015. The soln. was frozen and dried by lyophilization. A dry powder was obtained which was reconstituted before use with double distd. sterile pyrogen-free water. Multilamellar liposomes were formed; Loading efficiency of HBsAg was 97%. "Empty liposomes" were prepd. similarly by mixing 1 vol of aq. soln. of 0.9% NaCl with 1 vol of lipid soln. in tertiary butanol. The extent of HBsAg exposure on the liposome surface of the sample and

- liposome size was detd. The titer of antibodies which was developed was high and sufficient to protect against infection by HBV.
- IT 9001-28-9, Factor IX
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of vesicles loaded with biol. structures and biopolymers and/or oligomers)
- IC ICM A61K009-127
ICS C12N011-02; G01N033-544; C07K017-02
- NCL 424450000
- CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 15
- ST vaccine vesicle biopolymer oligomer; phospholipid vaccine vesicle biopolymer oligomer; liposome vaccine biopolymer oligomer
- IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hepatitis B surface; prepn. of vesicles loaded with biol. structures and biopolymers and/or oligomers)
- IT Drug delivery systems
(liposomes; prepn. of vesicles loaded with biol. structures and biopolymers and/or oligomers)
- IT Antitumor agents
(melanoma; prepn. of vesicles loaded with biol. structures and biopolymers and/or oligomers)
- IT B cell (lymphocyte)
Cryoprotectants
Melanoma
Physiological saline solutions
Vaccines
(prepn. of vesicles loaded with biol. structures and biopolymers and/or oligomers)
- IT Antibodies
Antisense RNA
Biopolymers
Complement
DNA
Enzymes, biological studies
Hormones, animal, biological studies
Oligomers
Phospholipids, biological studies
Zymogens
mRNA
tRNA
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of vesicles loaded with biol. structures and biopolymers and/or oligomers)
- IT Phospholipids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(soya; prepn. of vesicles loaded with biol. structures and biopolymers and/or oligomers)
- IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(surface; prepn. of vesicles loaded with biol. structures and biopolymers and/or oligomers)
- IT Phospholipids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(unsatd.; prepn. of vesicles loaded with biol. structures and biopolymers and/or oligomers)
- IT 75-65-0, tert-Butanol, uses
RL: NUU (Other use, unclassified); PEP (Physical, engineering or chemical process); PROC (Process); USES (Uses)
(prepn. of vesicles loaded with biol. structures and biopolymers and/or oligomers)
- IT 57-50-1, Sucrose, biological studies 57-88-5, Cholesterol, biological studies 63-42-3, Lactose 99-20-7, Trehalose 9001-28-9, Factor IX 18656-38-7, DMPC 61361-72-6, Dimyristoylphosphatidylglycerol
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of vesicles loaded with biol. structures and biopolymers and/or oligomers)

oligomers)
 REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L182 ANSWER 13 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1998:147190 HCAPLUS
 DOCUMENT NUMBER: 128:208915
 TITLE: Methods for the production of protein
 particles useful for delivery of
 pharmacological agents
 INVENTOR(S): Magdassi, Shlomo; Desai, Neil; Ferreri, Kevin;
 Soon-Shiong, Patrick
 PATENT ASSIGNEE(S): Vivorx Pharmaceuticals, Inc., USA; Magdassi, Shlomo;
 Desai, Neil; Ferreri, Kevin; Soon-Shiong, Patrick
 SOURCE: PCT Int. Appl., 26 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|--|----------|-----------------|----------|
| WO 9807410 | A1 | 19980226 | WO 1997-US14661 | 19970819 |
| W: | AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | |
| AU 9739169 | A1 | 19980306 | AU 1997-39169 | 19970819 |
| EP 938299 | A1 | 19990901 | EP 1997-936517 | 19970819 |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | |

PRIORITY APPLN. INFO.: US 1996-23968P P 19960819
 WO 1997-US14661 W 19970819

AB A method has been developed for the formation of submicron particles (nanoparticles) by heat-denaturation of proteins (such as human serum albumin) in the presence of multivalent ions (such as calcium). Also provided are novel products produced by the invention method. An appropriate concn. of multivalent ions, within a relatively narrow range of concns., induces the pptn. of protein in the form of colloidal particles, at a temp. which is well below the heat denaturation temp. of the protein (as low as 60 .degree.C for serum albumin). Temps. at which invention method operates are sufficiently low to permit incorporation of other mols. (e.g., by co-pptn.), into submicron particles according to the invention, including compds. which cannot withstand high temps. Invention methods facilitate the prodn. of protein nanoparticles and microparticles contg. various mols. (such as nucleic acids, oligonucleotides, polynucleotides, DNA, RNA, polysaccharides, ribozymes, pharmacol. active compds., and the like) useful for therapeutic, diagnostic and other purposes. The addn. of multivalent cations serves both to induce pptn., and to allow linking of neg. charged mols., such as DNA, to the neg. charged protein. Microparticles and nanoparticles were formed from albumin in the presence of CaCl₂.

IT 9001-28-9, Factor IX
 RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
 (prodn. of protein particles useful for delivery of pharmacol. agents)
 IC ICM A61K009-14
 CC 63-6 (Pharmaceuticals)
 ST protein microparticle drug delivery
 IT Agglutinins and Lectins
 RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

- (galactose-binding, galaptin; prodn. of protein particles useful for delivery of pharmacol. agents)
- IT Cytokines
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(macrophage-activating factor; prodn. of protein particles useful for delivery of pharmacol. agents)
- IT Drug delivery systems
(microparticles; prodn. of protein particles useful for delivery of pharmacol. agents)
- IT Glycopeptides
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(muramic-acid contg. diglycopeptides; prodn. of protein particles useful for delivery of pharmacol. agents)
- IT Drug delivery systems
(nanoparticles; prodn. of protein particles useful for delivery of pharmacol. agents)
- IT Antitumor agents
Antiviral agents
Cations
- Denaturation**
(prodn. of protein particles useful for delivery of pharmacol. agents)
- IT Albumins, biological studies
Antibodies
Caseins, biological studies
Collagens, biological studies
DNA
Enzymes, biological studies
Fibrinogens
Fibronectins
Gelatins, biological studies
Glucocorticoids
Growth factors, animal
Hemoglobins
Immunoglobulins
Interferons
Interleukin 1
Interleukin 2
Lactalbumins
Laminins
Macrophage migration inhibitory factor
Nucleic acids
Ovalbumin
Polysaccharides, biological studies
Proteins, general, biological studies
RNA
Ribozymes
Transferrins
Transforming growth factors
Tumor necrosis factors
Vitronectin
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(prodn. of protein particles useful for delivery of pharmacol. agents)
- IT Macroglobulins
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(.alpha.2-; prodn. of protein particles useful for delivery of pharmacol. agents)
- IT 50-56-6, Oxytocin, biological studies 665-66-7, Amantadine hydrochloride 7439-89-6D, Iron, ions, biological studies 7440-26-8D, Technetium, ions, biological studies 7440-54-2D, Gadolinium, ions, biological studies 8001-27-2, Hirudin 9000-92-4, Amylase 9001-05-2, Catalase 9001-27-8, Factor VIII 9001-28-9, Factor IX 9001-62-1, Lipase 9001-63-2, Lysozyme 9001-75-6, Pepsin 9002-01-1, Streptokinase 9002-07-7, Trypsin 9004-07-3, Chymotrypsin 9004-10-8, Insulin,

biological studies 9007-12-9, Calcitonin 9026-93-1, Adenosine deaminase 9035-68-1, Proinsulin 9035-81-8, Antitrypsin 9039-53-6, Urokinase 9054-89-1, Superoxide dismutase 11096-26-7, Erythropoietin 14127-61-8, Calcium ion, biological studies 14701-22-5, biological studies 15158-11-9, biological studies 16397-91-4, Manganese ion (Mn2+), biological studies 22537-22-0, Magnesium ion, biological studies 22537-23-1, Aluminum ion, biological studies 22537-39-9, Strontium ion, biological studies 22541-12-4, Barium ion, biological studies 22541-53-3, biological studies 23713-49-7, Zinc ion, biological studies 30516-87-1, Zidovudine 36505-84-7, Buspirone 36791-04-5, Ribavirin 37228-64-1, Glucocerebrosidase 50924-49-7, Mizoribine 51110-01-1, Somatostatin 59277-89-3, Acyclovir 60940-34-3, Ebselen 61912-98-9, Insulin-like growth factor 62031-54-3, Fibroblast growth factor 62229-50-9, Epidermal growth factor 62683-29-8, Colony stimulating factor 70641-51-9, Edelfosine 79831-76-8, Castanospermine 93135-89-8, Methoxatone 139639-23-9, Tissue plasminogen activator 142864-19-5, Enlimomab

RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(prodn. of protein particles useful for delivery of pharmacol. agents)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L182 ANSWER 14 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1987:464761 HCAPLUS

DOCUMENT NUMBER: 107:64761

TITLE: Interactions of polymerizable phosphatidylcholine vesicles with blood components: relevance to biocompatibility

AUTHOR(S): Bonte, F.; Hsu, M. J.; Papp, A.; Wu, K.; Regen, S. L.; Juliano, R. L.

CORPORATE SOURCE: Med. Sch., Univ. Texas, Houston, TX, 77225, USA

SOURCE: Biochimica et Biophysica Acta (1987), 900(1), 1-9
CODEN: BBACAQ; ISSN: 0006-3002

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The biocompatibility of polymerizable phosphatidylcholine bilayer membranes in liposome form for possible use in drug carrier systems or as surface coatings for biomaterials was studied. The SH-based polymerizable lipid 1,2-bis[1,2-(lipoyl)dodecanoyl]-sn-glycero-3-phosphocholine (dilipoyl lipid, DLL) and the methacrylic deriv.-based lipid 1,2-bis[(methacryloyloxy)dodecanoyl]-sn-glycero-3-phosphocholine (dipolymerizable lipid, DPL) bound complex mixts. of serum proteins with IgG being the most abundant bound component. DPL vesicles and anionic vesicles bound substantially more protein than other vesicle types. Polyimd. DPL vesicles uniquely bound a protein of about 53 kDa which was not bound to other types of phosphatidylcholine liposomes. Likewise polyimd. DPL vesicles, but not other types of phosphatidylcholine vesicles, caused a marked alteration in coagulation as measured by activated partial thromboplastin time and prothrombin time tests; this effect was due to binding and depletion of clotting factor V by the DPL polyimd. vesicles. Polyimd. DPL liposomes and DLL liposomes in polyimd. or nonpolyimd. form, were without substantial effect on platelet aggregation. However, DPL nonpolyimd. vesicles, while not causing aggregation, did impair ADP-induced aggregation of platelets. Thus, SH based polymerizable lipids of the DLL type may be very suitable for in vivo use in the contexts of drug delivery systems or biomaterials development. Methacryloyl-based lipids of the DPL type seem to display interactions with the hemostatic process which militate against their in vivo utilization.

IT 113189-02-9

RL: BIOL (Biological study)

(polymerizable phosphatidylcholines effect on)

CC 63-5 (Pharmaceuticals)

Section cross-reference(s): 1

ST phosphatidylcholine polymn biocompatibility; biomaterial coating polymn

phosphatidylcholine; liposome drug carrier biomaterial coating

IT Blood platelet

- (aggregation of, on polymerizable phosphatidylcholines)
- IT Phosphatidylcholines, biological studies
RL: BIOL (Biological study)
(liposomes contg. polymerizable., blood compatibility of, for drug carriers and biomaterial coatings)
- IT Proteins, biological studies
RL: BIOL (Biological study)
(of blood, polymerizable phosphatidylcholine binding by)
- IT Haptoglobins
RL: BIOL (Biological study)
(polymerizable phosphatidylcholine binding by)
- IT Prosthetic materials and Prosthetics
(polymerizable phosphatidylcholine coatings for, blood compatibility of)
- IT Albumins, biological studies
Fibrinogens
Macroglobulins
Transferrins
RL: BIOL (Biological study)
(polymerizable phosphatidylcholines binding by)
- IT Liposome
(polymerizable phosphatidylcholines, blood compatibility of, for biomaterial coating)
- IT Lipoproteins
RL: BIOL (Biological study)
(E, polymerizable phosphatidylcholines binding by)
- IT Pharmaceutical dosage forms
(liposomes, polymerizable phosphatidylcholine vehicles for, blood compatibility of)
- IT Globulins, biological studies
RL: BIOL (Biological study)
(.gamma.-, polymerizable phosphatidylcholines binding by)
- IT 80294-17-3 104807-08-1
RL: BIOL (Biological study)
(blood compatibility of liposomes contg., for drug carriers and biomaterial coatings)
- IT 9001-24-5, Blood coagulation factor V 9001-25-6, Blood coagulation factor VII 113189-02-9
RL: BIOL (Biological study)
(polymerizable phosphatidylcholines effect on)
- IT 79605-84-8 104778-79-2
RL: BIOL (Biological study)
(polymerizable, biocompatibility of liposomes contg., for drug carriers and biomaterial coatings)

L182 ANSWER 15 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1984:588884 HCAPLUS

DOCUMENT NUMBER: 101:188884

TITLE: Behavior of blood proteins at the interface with procoagulant phospholipids and anticoagulant heparin or polymeric biomaterials: a fluorescence study
AUTHOR(S): Dachary, J.; Dulos, E.; Faucon, J. F.; Boisseau, M. R.; Dufourcq, J.

CORPORATE SOURCE: Cent. Rech. Paul Pascal, Domaine Univ., Talence, 33405, Fr.

SOURCE: Colloids and Surfaces (1984), 10, 91-9

CODEN: COSUD3; ISSN: 0166-6622

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Changes in the fluorescence of factors IX and II in the presence of Ca at procoagulant phospholipid interfaces suggest a conformational change of the proteins upon binding. Shifts of transition temp. of phosphatidylcholine-phosphatidylserine mixts. towards those of the pure lecithin component when Ca and coagulation factors are added suggest that lateral phase sepn. does exist. The higher resonance-energy transfer efficiency with charged pyrene-labeled phospholipids leads to the conclusion that within the membrane, factor II and IX binding sites are

domains of phosphatidylserine. Ca-independent phospholipid binding, selective for phosphatidylserine, is well documented and is proposed to be mediated by electrostatic forces between the arginine and lysine residues of the proteins and the neg. charges of the phosphatidylserine. The binding of heparin or the synthetic anticoagulant polystyrene (bearing SO₃²⁻ and glutamic acid groups) with antithrombin or thrombin induces different fluorescence changes in these proteins which cause local changes in the tryptophan residues of the proteins upon binding. The interaction of heparin with various mixts. of thrombin and antithrombin indicates that heparin does not modify the structure of the preformed thrombin-antithrombin complex. as far as can be seen by spectrofluorimetry.

- IT 9001-28-9
RL: BIOL (Biological study)
(procoagulant phospholipids interaction with human, protein conformation in relation to)
- CC 13-5 (Mammalian Biochemistry)
Section cross-reference(s): 7
- ST phospholipid coagulation factor interaction; heparin coagulation factor interaction; anticoagulant coagulation factor interaction; polymer anticoagulant coagulation factor interaction; blood clotting factor phospholipid interaction
- IT Phosphatidylserines
RL: BIOL (Biological study)
(liposomes contg. phosphatidylcholine and, blood-coagulation factors II and IX of human interaction with, protein conformation in relation to)
- IT Phosphatidylcholines, biological studies
RL: BIOL (Biological study)
(liposomes contg. phosphatidylserine and, blood-coagulation factors II and IX of human interaction with, protein conformation in relation to)
- IT **Conformation and Conformers**
(of blood-coagulation factors II and IX of human, procoagulant phospholipid binding effect on, antithrombin and thrombin interactions with heparin in relation to)
- IT **Molecular association**
(of blood-coagulation factors II and IX of humans with procoagulant phospholipids)
- IT Phase transition
(of phosphatidylcholine and phosphatidylserine, binding of blood-coagulation factors II and IX of human effect on)
- IT **Liposome**
(phosphatidylcholine-phosphatidylserine, blood-coagulation factors II and IX of human binding to)
- IT Phospholipids
RL: BIOL (Biological study)
(procoagulant, blood-coagulation factors II and IX of human binding to, protein conformation response to)
- IT 9000-94-6
RL: BIOL (Biological study)
(III, heparin interaction with, of human, protein conformation in relation to)
- IT 9005-49-6, biological studies
RL: BIOL (Biological study)
(antithrombin III and thrombin III of human interaction with, protein conformation in relation to)
- IT 56-86-0D, polymer with polystyrene deriv. 9003-53-6D, deriv., polymer with glutamic acid
RL: BIOL (Biological study)
(antithrombin III and thrombin of human interaction with, protein conformation in relation to)
- IT 7440-70-2, biological studies
RL: BIOL (Biological study)
(blood-coagulation factors II and IX of human interaction with procoagulant phospholipids in presence of)
- IT 9002-04-4
RL: BIOL (Biological study)
(heparin interaction with, of human, protein conformation in relation to)

- to)
- IT 3036-82-6
RL: BIOL (Biological study)
(liposomes contg. dimyristoylphosphatidylcholine and, blood-coagulation factors II and IX of human interaction with, protein conformation in relation to)
- IT 18656-38-7
RL: BIOL (Biological study)
(liposomes contg. dipalmitoylphosphatidylserine and, blood-coagulation factors II and IX of human interaction with, protein conformation in relation to)
- IT 2644-64-6
RL: BIOL (Biological study)
(liposomes contg. phosphatidylserine and, blood-coagulation factor II of human interaction with, protein conformation in relation to)
- IT 9001-26-7 **9001-28-9**
RL: BIOL (Biological study)
(procoagulant phospholipids interaction with human, protein conformation in relation to)

L182 ANSWER 16 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1983:510607 HCAPLUS

DOCUMENT NUMBER: 99:110607

TITLE: Basic studies on oral and rectal administration of factor IX **concentrate** preparation

AUTHOR(S): Sakuragawa, Nobuo; Takahashi, Kaoru; Horikoshi, Isamu; Ueno, Masaharu

CORPORATE SOURCE: Cent. Clin. Lab., Toyama Med. Pharm. Univ., Toyama, Japan

SOURCE: Nippon Ketsueki Gakkai Zasshi (1983), 46(1), 190-6
CODEN: NKGZAE; ISSN: 0001-5806

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The stability of a factor IX [**9001-28-9**] conc. and its enclosure in liposomes for oral and rectal administration were investigated. Factor IX was stable at pH 8.0, and also stable at pH 7.0 by the addn. of aprotinin [9087-70-1]. Factor IX conc. itself contains activated coagulation factors, which convert prothrombin into thrombin spontaneously. This prepn. was stabilized by the addn. of aprotinin. The trapping rate of aprotinin by liposome was as low as 5.6%. The coagulation factors (100 and 400 units of factor IX) could be transferred into the blood efficiently with either oral administration or rectal application in dogs.

IT **9001-28-9**

RL: BIOL (Biological study)
(conc., stability and liposome encapsulation of, for oral and rectal administration)

CC 63-5 (Pharmaceuticals)

ST factor IX conc oral rectal; aprotinin factor IX conc; liposome factor IX conc

IT Digestive tract

(factor IX absorption by)

IT **Liposome**

(factor IX conc. encapsulation by)

IT Intestine, metabolism

(rectum, factor IX absorption by)

IT **9001-28-9**

RL: BIOL (Biological study)
(conc., stability and liposome encapsulation of, for oral and rectal administration)

IT 9087-70-1

RL: BIOL (Biological study)
(factor IX conc. stability by)

L182 ANSWER 17 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1982:588254 HCAPLUS

DOCUMENT NUMBER: 97:188254

TITLE: Pharmaceutical composition for oral administration
containing **coagulation** factor VIII
or IX
INVENTOR(S): Horikoshi, Isamu; Sakuragawa, Nobuo; Ueno, Masaharu;
Takahashi, Kaoru
PATENT ASSIGNEE(S): Dainippon Pharmaceutical Co., Ltd. , Japan
SOURCE: U.S., 6 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|-------------|------|----------|-----------------|----------|
| US 4348384 | A | 19820907 | US 1981-309269 | 19811007 |
| JP 57070814 | A2 | 19820501 | JP 1980-144508 | 19801017 |
| JP 03000366 | B4 | 19910107 | | |
| JP 57179122 | A2 | 19821104 | JP 1981-65685 | 19810428 |
| JP 03000851 | B4 | 19910109 | | |

PRIORITY APPLN. INFO.: JP 1980-144508 19801017
JP 1981-65685 19810428

- AB An oral prepn. for the treatment of hemophilia A or B consists of blood coagulation factor VIII [9001-27-8] or factor IX [9001-28-9] and a protease inhibitor incorporated in liposomes and (or) encapsulated in enteric capsules. The product provides for absorption of the coagulation factor from the intestinal tract without significant decompn. Thus, liposomes were prepd. from egg yolk lecithin contg. 5% alc. phosphatidic acid and a pH 7 phosphate buffer soln. of factor VIII (3000 units); aprotinin [9087-70-1] was added and the liposome suspension was washed with NaCl soln., cooled, centrifuged, and the liposomes were dried. Intestinal capsules were packed with 10 mL liposomes contg. 1000 units of factor VIII and 17,000 units aprotinin to give 50 units of factor VIII/capsule.
- IT 9001-28-9
RL: BIOL (Biological study)
(enteric-encapsulated liposomes contg. aprotinin and, for oral hemophilia treatment)
- IC A61K035-14
NCL 424101000
CC 63-3 (Pharmaceuticals)
ST blood coagulation factor liposome oral; hemophilia oral coagulation factor
- IT **Liposome**
(blood coagulation factors VIII and IX incorporated in, for oral hemophilia treatment)
- IT Phosphatidic acids
RL: BIOL (Biological study)
(calcium salts, liposomes contg. egg yolk lecithin and, for enteric-encapsulated blood coagulation factors, for hemophilia treatment)
- IT Lecithins
RL: BIOL (Biological study)
(egg yolk, enteric-coated liposomes contg. phosphatidic acids and, for blood coagulation factors)
- IT Intestine, metabolism
(liposome-incorporated blood coagulation factors VIII and IX absorption by, from capsules)
- IT Phosphatidic acids
RL: BIOL (Biological study)
(liposomes contg. egg yolk lecithin and, for enteric-encapsulated blood coagulation factors, for hemophilia treatment)
- IT Hemophilia
(A, treatment of, with enteric-encapsulated liposomes contg. blood coagulation factors VIII and IX and protease inhibitor)
- IT Hemophilia
(B, treatment of, with enteric-encapsulated liposomes contg. blood coagulation factors VIII and IX and protease inhibitor)

IT 9001-27-8 **9001-28-9**
 RL: BIOL (Biological study)
 (enteric-encapsulated liposomes contg. aprotinin and, for oral hemophilia treatment)

IT 9087-70-1
 RL: BIOL (Biological study)
 (enteric-encapsulated liposomes contg. blood coagulation factors VIII or IX and, for hemophilia treatment)

L182 ANSWER 18 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1982:550625 HCAPLUS
 DOCUMENT NUMBER: 97:150625
 TITLE: Oral and rectal administration to beagle dogs of factor IX **concentrates**
 AUTHOR(S): Sakuragawa, Nobuo; Takahashi, Kaoru; Horikoshi, Isamu; Ueno, Masaharu
 CORPORATE SOURCE: Cent. Lab., Toyama Med. Pharm. Univ., Toyama, Japan
 SOURCE: Saishin Igaku (1982), 37(7), 1414-18
 CODEN: SAIGAK; ISSN: 0370-8241
 DOCUMENT TYPE: Journal
 LANGUAGE: Japanese

AB factor IX [9001-28-9] was stable at pH 8.0, and addn. of aprotinin [9087-70-1] stabilized it even at pH 7.0. Factor IV was sealed into liposomes more efficiently on addn. of Ca and stearylamine [124-30-1].

IT **9001-28-9**
 RL: BIOL (Biological study)
 (concs., stabilization and liposome encapsulation of)

CC 63-3 (Pharmaceuticals)
 ST factor IX conc; liposome factor IX conc; aprotinin factor IX conc
 IT **Liposome**
 (blood-coagulation factor IX encapsulation by)

IT 9087-70-1
 RL: BIOL (Biological study)
 (blood coagulation factor IX conc. stabilization by)

IT 7440-70-2, biological studies
 RL: BIOL (Biological study)
 (blood coagulation factor IX encapsulation in liposomes in presence of)

IT 124-30-1
 RL: BIOL (Biological study)
 (blood coagulation factor IX encapsulation in liposomes with)

IT **9001-28-9**
 RL: BIOL (Biological study)
 (concs., stabilization and liposome encapsulation of)

L182 ANSWER 19 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 1982:223071 HCAPLUS
 DOCUMENT NUMBER: 96:223071
 TITLE: Studies on oral administration of **concentrated factor IX** preparation
 AUTHOR(S): Ueno, Masaharu; Horikoshi, Isamu; Takahashi, Kaoru; Sakuragawa, Nobuo
 CORPORATE SOURCE: Dep. Hosp. Pharm., Toyama Med. Pharm. Univ., Toyama, 930-01, Japan
 SOURCE: Yakugaku Zasshi (1982), 102(2), 202-6
 CODEN: YKKZAJ; ISSN: 0031-6903
 DOCUMENT TYPE: Journal
 LANGUAGE: Japanese

AB blood-coagulation factor IX [9001-28-9] was stable at 4-25.degree. in mildly alk. solns. and was effectively encapsulated in liposome preps. contg. 5% stearylamine or 0.02 M Ca²⁺; oral administration of the liposome-entrapped factor IX shortened clotting time in dogs. The transformation of prothrombin [9001-26-7] into thrombin [9002-04-4] was inhibited by adding phosphatidylcholines (250 mg) or 50,000 units aprotinin [9004-04-0]. The intestinal absorption of factor II, VII [9001-25-6], IX, and X [9001-29-0] is described.

IT **9001-28-9**

RL: BIOL (Biological study)
 (liposome-entrapped, oral administration of)
 CC 63-3 (Pharmaceuticals)
 ST factor IX liposome oral prepn
 IT **Liposome**
 (blood-coagulation factor IX encapsulated by)
 IT Phosphatidylcholines, biological studies
 RL: BIOL (Biological study)
 (prothrombin transformation into thrombin inhibition by)
 IT 9002-04-4
 RL: FORM (Formation, nonpreparative)
 (formation of, from prothrombins, inhibitors of)
 IT 9001-25-6 9001-29-0
 RL: PROC (Process)
 (intestine absorption of)
 IT **9001-28-9**
 RL: BIOL (Biological study)
 (liposome-entrapped, oral administration of)
 IT 9087-70-1
 RL: BIOL (Biological study)
 (prothrombin transformation into thrombin inhibition by)
 IT 9001-26-7
 RL: PROC (Process)
 (transformation of, into thrombin, inhibitors for)

=> d ibib abs 20

L182 ANSWER 20 OF 20 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
 ACCESSION NUMBER: 1989-220140 [30] WPIDS
 CROSS REFERENCE: 1987-095635 [14]; 1990-382605 [51]
 DOC. NO. NON-CPI: N1989-167754
 DOC. NO. CPI: C1989-097845
 TITLE: Heat processing system - esp. useful for sterilising
 blood plasma prods., subjects prods. to microwave energy
 after **dielectric** enhancing additive addn..
 DERWENT CLASS: D22 P34 S05
 PATENT ASSIGNEE(S): (CHAR-I) CHARM S E
 COUNTRY COUNT: 1
 PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|------------|------|----------|-----------|----|----|
| US 4839142 | A | 19890613 | (198930)* | | 7 |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|------------|------|---------------|----------|
| US 4839142 | A | US 1987-71733 | 19870708 |

PRIORITY APPLN. INFO: US 1985-782019 19850930; US 1987-71733 19870708

AN 1989-220140 [30] WPIDS
 CR 1987-095635 [14]; 1990-382605 [51]
 AB US 4839142 A UPAB: 19940307

Treatment process for heat-sensitive biological fluid (I) comprises preteinaceous material and a pathogenic organism is claimed. The method comprises (a) rapidly heating (I) with a dielectric constant of more than 90 at a rate of more than 25 deg.C per sec., to a preselected temp. using microwave heating energy; (b) holding (I) at the preselected temp. for up to about 2 secs.; (c) rapidly cooling to a preselected lower temp; and (d) circulating the heated (I) while rapidly heating, holding and rapidly cooling.

The heating, holding and cooling time periods are sufficiently short and the preselected heating temp. and the lower temp. are sufficient not

to effect the desirable properties of the proteinaceous material but sufficient for at least the partial destruction of the pathogenic organism. Also claimed is a method for heating blood plasma or serum to destroy an infectious agent which comprises adding a dielectric salt to increase the dielectric constant to 90-300, then rapidly heating to at least 60 deg.C for less than 0.1 sec. by microwave heating energy to destroy the agent without altering albumin or blood clotting

Factors VIII and IX of the blood plasma or serum. The

high temp., short time heat process system is also claimed.

USE/ADVANTAGE - The method may be used to sterilise a wide variety of biological fluids, such as microbial media, tissue culture media, suspensions which cannot be sterilised employing ultrafiltration, such as liposomes or collagens, vaccines, mother's milk, fermentation media and cell culture media. The method may also be used to sterilise blood plasma to selectively destroy agents, such as viruses (e.g. hepatitis and AIDS), and microplasma. The method may also be used to sterilise blood plasma to selectively destroy agents, such as viruses (e.g. hepatitis and AIDS) and microplasma. The method permits continuous and rapid heating of (I) and is useful for small scale laboratory prodn. .

Dwg.1/1